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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,449	10/06/2003	Liwen Huang	1438.01	4490

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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/680,449	HUANG ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *1-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/8/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

Applicant's response filed 25 September 2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 25 May 2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

With entry of the amendment filed on 25 September 2006, Claims 1–34 are pending. Claims 1-15 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 112, second paragraph—withdrawn

The rejection of Claims 30 and 34 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicant's amendments to the claims.

Claim Rejections - 35 USC § 112, first paragraph—withdrawn

The rejection of Claims 16–34 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 18–20, 24–26, and 31–34 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Broadest reasonable interpretation of independent claim 18 includes a kit comprising a human being. Claims 19, 20, 24–26 and 31–34 are rejected therefore due to their dependence on claim 18.

Inserting the term "non-human" before the term "organisms" would be remedial.

Claim Rejections - 35 USC § 103—new

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 16–34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sijen et al. (2001) *Cell* 107:465–476; Pal-Bhadra et al. (1998) *Cell* 99: 35–46; Voinnet et al. (1998) *Cell* 95:177–187; Fire et al. (1990) *Gene* 93:189–198; Kennerdell et al. (1998) *Cell* 95:1017-1026; and Elbashir et al. (2001) *Nature* 411:494-498.

The claims are drawn to a kit comprising a plurality of expression vectors, cells, or organisms, each comprising an expression cassette that directs the expression of a chimeric RNA transcript that has a subject RNA operably linked to a universal target RNA, wherein at least two of the plurality of expression vectors, cells, or organisms express chimeric RNA transcripts with different subject RNAs, and wherein all of said plurality of expression vectors, cells, or organisms express chimeric RNA transcripts with the same universal target RNA; and a universal interfering RNA targeting said universal target RNA, or an interfering RNA

transcription vector that directs the expression of said universal interfering RNA, wherein said universal interfering RNA is an siRNA or shRNA.

The specification defines a "chimeric RNA transcript" as an RNA transcript comprising a subject RNA operably linked to a universal target RNA to create a single RNA that does not naturally occur in nature (page 16, bottom).

Sijen et al. teach materials and methods for investigating transitive RNAi and gene function in *C. elegans,* comprising the use of transgenic *C. elegans* organisms and vectors expressing chimeric GFP-encoding transcripts (see Fig. 3). A proposed model for transitive RNAi is presented in Fig. 1. The authors teach that the model leads to a number of testable predictions, wherein an initial trigger dsRNA targeted to one region of an mRNA will lead to the production of secondary dsRNAs directed to other, possibly, upstream regions of the same or homologous target RNA (page 466). This is schematically depicted in Fig. 1B and 1C.

To compile direct evidence for transitive RNAi, Sijen et al. constructed two different vectors: the first expressing GFP fused to lacZ; the second, GFP alone (Fig. 3). In the first vector, the GFP gene is further fused to a nuclear location signal (NLS), while in the second vector GFP is further fused to a mitochondrial location signal (Mito). Using dsRNA targeted to the lacZ region, Sijen et al. show that lacZ-specific dsRNA inhibited the expression of GFP in both the mitochondrially targeted and nuclear targeted transcripts, indicating that a single dsRNA trigger directed to a downstream sequence could inhibit the expression of two different transcripts. The result is attributed to the production of secondary RNAi against the upstream sequence, GFP, induced or triggered by a single dsRNA targeting the downstream sequence, lacZ (Fig. 3, page 468).

As further proof of transitive RNAi, Sijen et al. created transgenic nematodes comprising an *unc-22::gfp* transgene. Sijen et al. then show that injection of GFP-specific dsRNA into wild-type animals produced no phenotype, whereas injection of GFP-specific dsRNA into transgenic animals expressing an *unc-22::gfp* transgene produced a twitching phenotype characteristic of inhibition of *unc-22* (Fig. 4C, and page 468, left column, bottom). The results provide further evidence of transitive RNAi in *C. elegans.* Further tests with in-frame deletion mutants provide yet further evidence for transitive RNAi, and lead Sijen et al. to state at page 468, right column, that these experiments demonstrate that transitive RNAi is not limited to transgene targets, but can also target physiological expression of cellular genes.

Altogether then, Sijen et al. demonstrate how a single interfering dsRNA can inhibit the expression of at least three different, non-naturally occurring transcripts, and at least two different subject RNAs linked to a common target, GFP. In this case, Sijen et al. show and implicitly suggest that linking a common, non-naturally occurring sequence such as GFP or lacZ, to different genes, such as unc-22 and GFP, can render such sequences susceptible to RNAi via a single dsRNA targeted to the GFP or any other down stream sequence. The tests were designed to study the transitive RNAi phenomenon in *C. elegans,* but Sijen et al. suggest implicitly and explicitly that similar studies might be carried out to further elucidate the biochemical mechanisms of transitive RNAi in *C. elegans* as well as other organisms, including *Drosophila* and plants. For instance, Sijen et al. state that the absence of an identified RdRP homolog in *Drosophila* and mammals suggests either (1) that other RNA copying enzymes are used in these systems for amplification or (2) that the primary siRNAs may be sufficient to produce detectable interference response (page 473 bridging to 474).

Sijen et al. state further, at page 474, left column, that "With or without an RNA copying process, a variety of additional amplification mechanisms may contribute to silencing. In this regard, it is of interest to note two previous examples of transitive silencing: Pal-Bhadra et al. observed examples of transitive silencing in *Drosophila*, while Voinnet et al. reported transitive silencing with a GFP transgene target in plants." "It will be of interest in the future to understand the breadth of different amplification events operating in gene silencing and their biological roles."

Thus, Sijen et al. clearly suggest further studies of transitive RNAi in other organisms as well as in *C. elegans*.

Importantly, Sijen et al. also explicitly recognize the value and utility of siRNAs for these types of studies. At page 471, for example, Sijen et al. teach that siRNAs (21-25 nt) may be used effectively in *C. elegans* to specifically reduce the expression of certain target genes (page 471), for example, to study the function of certain genes and their role in transitive RNAi. Sijen et al. explicitly refer to the teachings of Elbashir et al. regarding the material description and function of siRNAs in general (page 471).

Sijen et al. conclude by stating that "A number of extant models for gene silencing in plants propose an amplification step relying on chromosome-targeted effects." "It will be of interest in the future to understand the breadth of different amplification events operating in gene silencing and their biological roles" (page 474).

While Sijen et al. teach vectors and organisms comprising at least two different non-naturally occurring trancripts (unc-22::GFP and pSAK2, GFP-lacZ and pSAK4, GFP) and methods for silencing different non-homologous targets using interfering dsRNA directed to a

non-homologous down stream sequence operably linked to the non-homologous target, and while these experiments clearly suggest that one dsRNA can silence multiple different upstream targets linked to the same down stream target, Sijen et al. do not explicitly teach at least two different vectors or transgenic organisms in a single array or single experiment comprising at least two different subject RNAs linked to the same target, downstream sequence such as GFP or lacZ.

Fire et al. disclose a modular set of *lacZ* fusion vectors for studying gene expression in *Caenorhabditis elegans.* It is taught and shown that the vectors enable one to analyze the expression of several genes in the nematode *C. elegans.* It is taught that *lacZ* can be expressed in wide variety of different tissues and cell types, and that these vectors should be useful in studying gene expression both in *C. elegans* and other experimental systems. In particular, it is taught that the *lacZ* encoded enzyme, β-galactosidase, serves as a sensitive and reliable reporter for monitoring the expression of any fusion.

Fire et al. provide a detailed description of the materials and methods used to construct and manipulate the vectors for purposes of cloning and expression under a variety of conditions and in a range of different cell types and subcellular locations.

Accordingly, Fire et al. implicitly and explicitly suggest a wide variety possible uses for the vectors and libraries that have been and may be constructed with them.

Kennedell et al. teach that dsRNA interference may be a valuable system with which to understand aspects of gene function in many organisms (page 1018). Using RNAi to study gene function in *Drosophila.* Kennerdell et al. teach that a sequence shared between several closely related genes may interfere with several members of the same family. For example, Kennerdell et al. state that dsRNAs corresponding to the 5' UTRs of *fz* and *Dfz2* had no interfering activities

on their own, but dsRNAs corresponding to coding sequences shared by *fz* and *Dfz2* had weak but significant interfering activities (page 1022).

Kennerdell et al., therefore, imply that double-stranded, interfering RNA targeted to a single common sequence can inhibit the expression and function of more than one gene comprising that common sequence.

Kennerdell et al. teach that the mechanism of dsRNA interference is unknown, and if the mechanism is the same for flies and nematodes, then work from *C. elegans* points to a post-transcriptional mechanism (page 1023, left, top). Kennerdell et al. speculate that interference may involve an amplification step (page 1023). Therefore, Kennerdell et al. implicitly suggest further studies to investigate possible amplification mechanisms in these and other organisms.

Elbashir et al. teach the advantages, synthesis, and use of siRNAs in general for mediating gene-specific inhibition in flies and mammalian cells. Elbashir et al. teach in general that RNAi is an effective tool for studying gene function.

It would have been obvious to one of skill in the art at the time the instant invention was made to make and use vectors, cells, and transgenic organisms expressing different genes fused to a common reporter sequence or sequences such as *lacZ* and/or *gfp,* to study transitive RNAi in *C. elegans* and other organisms including *Drosophila* and plants, as suggested by Kennerdell et al. and Sijen et al. It would further have been obvious to make and use several different chimeric vectors, transgenic organisms and/or host cells, to define and elucidate transitive RNAi and/or amplification mechanisms in a variety of organisms. As part of the overall study, it would have been standard laboratory practice to produce and test several different expression constructs and/or organisms in compartments, such as 96-well plates, racks of test tubes, multi-well culture

plates and or petri-dishes, depending on the experiment and organism, and as part of the overall design choice.

One would have been well motivated given that both Sijen et al. and Kennerdell et al. emphasize the importance of the amplication effect and possible systemic spread of RNAi in some organisms. One of skill in the art would have been motivated to define these mechanisms and more clearly understand the role it plays in naturally occurring RNAi, as part of viral defense, for example in plants and/or higher eukaryotes. One would have been motivated to make and test several different configurations of transgenes and vectors encoding chimeric transcripts, and to arrange such constructs in an organized fashion, compartmentalized as per normal laboratory practice, in well-marked containers, wells, test tubes, microtiter plates and so on, to define the particular molecular requirements of transitive RNAi in any given organism. Thus several hundred if not thousands of possible configurations and conditions would be provided for study.

One would have had a reasonable expectation of success given that Fire et al. show how to clone and express hundreds of gene of different genes as fusions to *lacZ,* a well defined and easily visualized reporter gene, against which interfering RNAs are easily prepared and readily available. Alternatively or in addition, one of skill would have had easy access to GFP encoding constructs and would have known how to manipulate and construct many different GFP encoding constructs for studying transitive RNAi, based on the teachings and exemplary embodiments given in Sijen et al., Par-Bhadra et al., and Voinnet et al., and as suggested by Kennerdell et al.

Accordingly, the Examiner submits that the instant invention would have been prima facie obvious to one of skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LVW
Examiner, Art Unit 1635
November 16, 2006

/J. Schultz/
JAMES SCHULTZ, PH.D.
Supervisory PRIMARY EXAMINER

SEAN McGARRY
PRIMARY EXAMINER
1635